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## THE ISOLATION OF CRYSTALLINE PROGESTIN<sup>1</sup>

By DR. W. M. ALLEN

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THE actual isolation of a hormone in pure form, determination of its chemical formula or even its synthesis is oftentimes simpler than the basic researches necessary to show that a given physiological condition exists only when a certain hormone is acting. The hormonal rôle of the corpus luteum and the isolation and synthesis of its hormone are no exceptions to this dictum, and for this reason I must describe briefly some of the work, already classical, showing that this little structure is a gland of great importance in the propagation of the race.

In all the higher forms of animal life reproduction is brought about by union of specialized cells of the two sexes, but the development of the fertilized ovum

<sup>1</sup> Address at the meeting of the American Chemical Society, New York, April, 1935, on the occasion of the presentation of the first Eli Lilly and Company award in biological chemistry.

into a new animal is carried out in a variety of ways, depending on the type of individual. In birds, for example, the fertilized egg is incubated outside the mother's body and hence there can be no direct effect of the mother on her offspring after the egg has been laid. With mammals, on the other hand, the early development of the embryo is quite different, for in them the embryo must first be nourished within the body of the mother for a considerable length of time before it reaches a stage of development such that it can be born, and even then the young are so premature as to require suckling for some time. It is not surprising, therefore, that we find highly specialized structures in the mammalian female designed exclusively for use in rearing the young.

The differences between the reproductive organs and the reproductive processes of the lower animals and

the mammals have been appreciated of course, for many years, but it was not until the latter part of the last century that any attempt was made to study these differences in much detail. In fact, the modern school dealing with the physiology of reproduction owes its origin in part to a German embryologist, Born, who first fully appreciated the significance of the fact that the ovary of all mammals contains a special structure, known as the corpus luteum, which is not present in the lower forms of animal life. Purely by analogy he reasoned that this gland should have some relation to the development of the placenta and the intra-uterine growth of the embryo because it occurs only in those animals in which intra-uterine development takes place and because it reached its greatest size during pregnancy. He postulated, therefore, that removal of the corpus luteum should interrupt pregnancy. Unfortunately, Born did not live to try out this beautiful hypothesis, which marked the first step in our understanding of the intricate phases of mammalian reproduction; but he passed the idea on to one of his students, Ludwig Fraenkel.

The experiments by Fraenkel, which showed for the first time that the mammalian ovary had a function other than egg-bearing, were carried out in 1903. He showed by studies in rabbits that removal of the corpora lutea or the ovaries during the first few days of pregnancy invariably prevented a continuation of the pregnancy. At that time, these results evoked so much criticism that Fraenkel repeated them in 1910, but the findings were exactly the same, *i.e.*, the corpora lutea were indispensable for the continuation of pregnancy and his master's hypothesis was fully substantiated.

At this point a little digression into the anatomy of the rabbit will serve to clarify the experiments of Fraenkel and at the same time refresh our memory regarding the details of the mammalian ovary. The ovary contains numerous cystic structures, known as graffian follicles, which are lined with specialized cells and in which the ovum repose. These follicles gradually increase in size and eventually rupture, discharging the ovum into the abdominal cavity. From there they soon find their way, by procedures as yet unknown, into the fallopian tubes, where fertilization takes place. The fertilized ova then spend 4 days wandering down the tube and into the uterus where they grow and become attached by means of placentae. During this period of transportation the ovary has not been idle; the cells lining the collapsed follicle have increased in size, capillaries have grown in and a new structure, the corpus luteum, has been formed. This process always takes place following ovulation, so that the corpus luteum is invariably associated with the recently extruded ovum and the

young embryo. These bodies gradually increase in size and last for two weeks, unless fertilization takes place, in which event they persist throughout gestation, regression starting shortly before parturition takes place. These are the structures which Fraenkel removed and which he found so important in the normal continuation of pregnancy.

This pioneering work of Fraenkel was soon followed in 1907 by the work of Leo Loeb, which showed that during the first few days after ovulation the uterus is in a special physiological state whereby implantation is made possible. He found, using guinea pigs for the experiments, that if the uterus were traumatized on the seventh day after ovulation, a tumor would develop in the endometrium which was identical with the maternal portion of the placenta. This result could not be obtained at other times in the cycle and could never be obtained if the corpora lutea were removed at the time the uterus was injured.

In 1910, Ancel and Bouin began the work which produced a morphological explanation of Fraenkel's results by showing that the rabbit's uterus, while under the influence of the corpus luteum, undergoes very remarkable changes. They found that in the resting state, there were a few small glands, but when the corpus luteum appeared there was associated with its growth and persistence a remarkable change in the uterus. It became enlarged and congested, and its epithelium underwent great mitotic proliferation, resulting in a highly complicated picture. This specialized state was interpreted as being necessary for implantation of the fertilized ova. At other times (1910, 1924) they have shown that excision of the corpora lutea always prevents development of this endometrial proliferation.

We had, therefore, ample evidence that the uterus undergoes very special changes when under the influence of the corpus luteum, but as yet there was no complete explanation of why embryos failed to implant when the corpus luteum was removed, as in Fraenkel's experiments, since nobody had actually investigated the fate of the embryos under these circumstances. This phase of the subject was completed in 1928 by my chief, Dr. Corner. Again using rabbits, he was able to show that, if the corpora lutea were removed 18 hours after mating when the young embryos are already in the tubes, the embryos developed normally for about 4 days, but after that they immediately stopped growing and shrivelled up and disappeared. You will recall that with no corpora lutea present the endometrial proliferation discovered by Ancel and Bouin also failed to take place. It was only natural, therefore, to assume that the embryos died because the uterus had not been properly prepared for their reception, and that presumably one of

the functions of the proliferated endometrium was to nourish the embryos prior to implantation.

I have described these experiments of Fraenkel, Loeb, Aneel and Bouin, and Dr. Corner in some detail because each adds an important link in the chain indicating that the corpus luteum plays no small rôle in the processes of reproduction. To complete the chain of evidence that it was an endocrine gland it would only be necessary to prepare an extract of the corpus luteum which would induce in an animal without corpora lutea all the changes which the corpus luteum itself was known to produce. Specifically, an active corpus luteum extract would be expected to produce endometrial proliferation in the castrated rabbit, maintain pregnancy in a castrated pregnant rabbit and sensitize the uterus of a castrated guinea pig so that deciduomata would be produced following mechanical trauma, as in the experiments of Leo Loeb.

With these objects in view in 1927 Dr. Corner and I began extracting pigs' corpora lutea hoping to assay the extracts by their capacity to produce endometrial proliferation in the immature rabbit. (We chose the immature rabbit because young animals never have corpora lutea in their ovaries, and hence no difficulty would be experienced with the rabbit's own corpus luteum.) The method of preparation was deliberately planned after a procedure used by Hermann in 1915, since apparently he obtained active extracts in some cases.

At this point I shall have to digress once more to explain that a large number of people, in the interim following the work of Fraenkel, Loeb and Aneel and Bouin, had prepared extracts of placenta, ovaries and follicle fluid and many had obtained preparations which would bring the uterus of an immature or castrated animal into full sexual maturity after only a few days' injection. This work is fully as fascinating and important as that dealing with the corpus luteum, but I shall have to leave it by saying that the work of Edgar Allen and Doisy led to the isolation in pure form (1930) of a hormone from the urine of pregnant women which had all the properties of the earlier extracts, in so far as their ability to cause growth of the uterus and vagina were concerned. However, study of these oestrogenic extracts, called that because they induced characteristically those changes found during oestrus or heat, by Asdell and Marshall (1927) and Corner and Allen (1929) in the rabbit, and Loeb and Kountz (1928) and Ebhardt (1928) in the guinea pig, showed that they do not produce the changes in the uterus which are characteristic of the corpus luteum phase of the cycle. It was apparent, therefore, that the extracts of Hermann (1915), which according to his own illustrations must have contained an active corpus luteum hormone in

some cases, had something in them quite different from the substance isolated by Doisy. We were led, therefore, to attempt to repeat Hermann's work, but this proved to be quite impossible because he was not aware that in most cases his extracts contained the oestrogenic hormone rather than a special corpus luteum hormone.

By using an ordinary aleoholic extract we were able after only about two or three months' work to prepare a crude extract which occasionally produced endometrial proliferation in young rabbits, but the results were so irregular, even though the method of preparation was kept constant, that in desperation we assumed that the fault lay with the test animal and not the extract. We then changed to an adult, recently castrated rabbit and when such an animal was injected with adequate doses of the extract perfect proliferation was obtained in every case, and if the animals were mated 18 hours before castration, and then injected daily for 5 days, normal embryos, as well as good proliferation, were obtained. In short, the evidence that the corpus luteum was an endocrine gland whose chief function was the preparation of the uterus for the implantation of the embryos was complete. At the same time Tatelbaum and Goldstein studied the effects of these extracts on the guinea pig's uterus following the experimental method of Leo Loeb. They found that it also sensitized the endometrium so that deciduomata could be produced following artificial trauma. Dr. Corner and I were also able to carry rabbits whose ovaries had been removed 18 hours after mating through to full term by the daily injection of the extract. The active principle was able therefore to substitute for the corpus luteum in every respect as far as its function was known at that time.

With this convincing evidence that the extracts really contained a hormone or active principle, we set about the task of trying to isolate the compound in pure form, assaying it by its ability to induce pregestational proliferation. We then developed a standard biological unit, named the hormone progestin, *i.e.*, a substance necessary for gestation, and began to fractionate the crude extract into different fractions. You will recall that we used aleoholic extracts. This means that we were dealing with the lipid fraction. The purification consisted essentially in separating all the known lipids without the use of alkali, because saponification caused complete inactivation. In this respect the hormone was quite different from the oestrogenic hormone isolated by Doisy because that could be treated vigorously with moderately strong alkali without any deleterious effect. The alcohol is boiled off and the residue extracted with ethyl ether, and an excess of acetone is added to the ether. This precipitates the phospholipids and causes marked puri-

fication. When the acetone ether is boiled down to dryness a thick syrupy oil is obtained which contains about 1 rabbit unit per half gram of solids, the solids being cholesterol, neutral fat and fatty acids. This oil is next dissolved in a fairly large volume of 70 per cent. methyl alcohol and chilled at  $-5^{\circ}$  C. for several hours, practically all the cholesterol and neutral fat being removed. The 70 per cent. alcohol is then distilled off and the aqueous remainder extracted with ethyl ether or petroleum ether, the hormone being obtained in a relatively pure condition, 1 rabbit unit equalling from 20 to 40 mg.

At this point it should be stated that these extracts really contained two hormones rather than one. We were assaying only the progestin, but at the same time we were extracting oestrin as well as progestin, since occasional tests by the Allen and Doisy method for oestrin showed that considerable amounts of this substance were invariably present. This meant that no physiological results obtained with these extracts could be said to be due to progestin alone, since both hormones were present. We, therefore, desisted from purification and developed a method for separating the oestrin from the progestin. The key to this separation was to be found in some data obtained on the distribution of progestin between 70 per cent. EtOH and petroleum ether (Allen and Meyer, 1933). We found that about 75 per cent. of the progestin remained in the alcohol and 25 per cent. was lost along with the majority of solids to the petroleum ether. Now, Doisy already had shown that the oestrogenic compound was retained in the alcohol even better. In fact, when the relative solubilities were computed, using the formula ordinarily used for the distribution of a substance between two immiscible solvents, we found that progestin was four times as soluble in 70 per cent. alcohol as in petroleum ether, and when Doisy's figures were subjected to similar mathematical analysis oestrin was found to be about twenty-five times as soluble in 70 per cent. alcohol as petroleum ether. This difference in solubility made a separation theoretically possible, but rather tedious because of the sparing solubility of progestin in petroleum ether, as compared to alcohol. However, a few additional facts such as the solubility of oestrin in dilute alcohol and its insolubility in petroleum ether led us to try separation between 35 per cent. alcohol and petroleum ether. When these maneuvers were carried out taking care to work over the petroleum ether twice, an excellent separation of oestrin and progestin was obtained. In fact, 95 per cent. of the oestrin was removed with no loss of progestin whatsoever.

Having thus removed the oestrin we returned to purification of the progestin fraction. This was accomplished by further distributions between dilute al-

cohol and petroleum ether and by freezing from absolute ether-petroleum ether at  $-70^{\circ}$  C. When this is done a copious yield of crystals is obtained, but they were no more potent than the mother liquors. Consequently we distilled the non-crystallizable oils in high vacuum in a specially designed apparatus which I'm sure Hill and Carruthers would recognize as a modification of their subliming apparatus. This has several advantages. The upper half, including the condenser, can be lifted out and the oil introduced into the well in ether solution. The ether can be evaporated off and the last traces pumped off, using a large rubber stopper to plug the upper end. After all solvent has been removed and all danger of splashing has passed, the upper half is replaced and the chamber evacuated. When the vacuum is about 0.0005 mm and temperature about  $100^{\circ}$ - $120^{\circ}$  a thick yellow wax sublimes. When this is dissolved in ethyl-ether-petroleum ether a considerable amount of crystals is obtained, and these are much more potent than the first lot. However, they are usually worked up together for convenience.

The crude crystals were quite potent, 2.5 mg usually being a rabbit unit. These were then subjected to fractional crystallization from ethyl ether-petroleum ether mixtures. Two different types of crystals were obtained. The less soluble ones were obviously impure and melted with decomposition at about  $160^{\circ}$ . From the mother liquors were obtained long prismatic needles which melted at  $116^{\circ}$  without decomposition and which were about three times as potent as the higher melting ones. This was quite encouraging, so we worked up another large batch of tissue, only to find that no needles were found, but that short thick prisms melting at  $125^{\circ}$  this time were very potent, and curiously enough these seemed to have the same potency as the needles, *i.e.*, about 1 mg to the rabbit unit. At this point we entered into a partnership with Dr. Wintersteiner, of Columbia University, whose expertness in micro analysis we hoped would help solve these apparent difficulties. When he fractionally crystallized a lot of 400 mgs of crude crystals he obtained four different compounds, which for the sake of convenience we called A, B, C and D. A melted at  $190^{\circ}$ . These were found to be quite inactive. B melted at  $128^{\circ}$  when pure, the prisms mentioned above, and were very potent. C melted at  $120.5$ - $121^{\circ}$  when pure, the long needles I originally obtained and they were also very potent. D melted at  $65$ - $74^{\circ}$  and was inactive.

These same compounds were then micro-analyzed and their molecular weight determined. The inactive compound was found to have the empirical formula  $C_{21}H_{34}O_2$  and the two active compounds  $C_{21}H_{30}O_2$  within limits of error of the methods. The two active

compounds gave identical disemicarbazenes and dioximes, and they had identical absorption curves with a maximum at 240 m $\mu$ . The compounds appeared, therefore, to be polymorphous forms of one and the same diketone, presumably containing at least one double bond. The inactive compound A was found to be a hydroxy ketone since it gave a mono-semicarbazone and a *p* nitro benzoate.

These results, therefore, were of considerable significance when we recall that pregnadiol  $C_{21}H_{36}O_2$ , a dialeohol, is found in the urine of pregnant women. What would be more logical than a series of compounds; progestin -  $C_{21}H_{30}O_2$ , a diketone with one double bond; pregnandione -  $C_{21}H_{32}O_2$ , a diketone, already known with no double bond; our oxyketone,  $C_{21}H_{34}O_2$ , and pregnadiol,  $C_{21}H_{36}O_2$ , all reduced products of the hormone. If so, our oxyketone should give pregnandione a known compound melting at 123°, but on oxidation it gave a diketone melting at 193°.

Once more I should like to digress and mention that at about the same time as our work on the pure substance appeared two German chemists, working independently, Dr. Butenandt and Dr. Slotta, reported the same chemical compounds. Their analyses and identification of the oxygens agreed perfectly with ours. Slotta's physiological studies of the potency of these two compounds were at variance with ours, rather seriously so. He found that full endometrial proliferation could not be obtained without the proper combination of the two different types of crystals, either form being inactive alone. Butenandt had no published data on the matter at that time. Recently, however, he has confirmed our results by showing that both crystals have the same potency. This adds very convincing evidence to the chemical evidence that the two crystalline forms are merely polymorphous modifications of one and the same substance.

I should like to show a few photographs of the two forms to show how different the same compound may appear. In general the needles are obtained when crystallizing from fairly dilute alcohol and prism when crystallizing from stronger alcohol. The melting points of these substances are also abnormal. The high melting variety on remelting will frequently melt at 120° and the low melting form will melt several degrees higher the second time. These findings do not occur regularly, however.

This about concludes the story as far as we are concerned, but I can not close without describing

briefly the beautiful conclusion which Dr. Butenandt has brought to the subject by developing in the space of only a few months the structure of progestin and a method of synthesis. I mentioned above the close similarity between the empirical formula of progestin and pregnadiol. Butenandt had already worked out the detailed structure of pregnadiol. This substance was then converted by oxidation to a diketone, pregnandione, then brominated and HBr removed, the result—progestin. And curiously enough the active substance also occurred in two crystalline forms which were identical in every respect with that isolated from pigs' ovaries. An even more beautiful synthesis was carried out using stigmasterol, a wax obtained from soybeans, as a starting point. This was changed to 3-oxy bis-nor cholenic acid by the method of Fernholz and then converted to an unsaturated oxy-ketone, which we may call pregnenolone. The double bond was protected by bromination and the resulting dibrom compound oxidized to a diketone. Again when the bromine was split out progestin was obtained. These findings leave little doubt that the compound isolated from the natural source is really the hormone and further that the same active substance has been synthesized from inactive compounds of known structure. The formula must be correct, unless those for pregnadiol and stigmasterol are incorrect, something which is rather unlikely.

Surely no person a few years ago would have predicted that the hormone progestin would ever be made from such a non-human source as soy-beans.

One final question, What will the hormone be used for? Only time can tell. If it is found never to have any therapeutic value the result will have been worth the chase, for it has helped immeasurably to clarify some phases of the reproductive processes and at the same time contributed something to the chemistry of the human body.

In conclusion, I wish to take this opportunity to express my appreciation to Dr. Corner, who provided the stimulus for my early interest in the subject, and who, by his patience, has encouraged me to continue with it; and to Dr. Wintersteiner who, because of his remarkable technical skill and chemical ingenuity, helped to bring order out of chaos. I also wish to thank most gratefully the Eli Lilly and Company for their part in making the award possible and the committee which saw fit to make me the first recipient of the award.

## OBITUARY

### JOHN WEINZIRL

JOHN WEINZIRL, professor of bacteriology and director of the McDermott Foundation at the Univer-

sity of Washington, died, after a week's illness, on June 26, 1935. He was a native of Wisconsin, having been born on September 10, 1870. He was educated

at River Falls Normal School and the University of Wisconsin (B.S. 1896, M.S. 1899, Ph.D. 1906). Some years later he spent a sabbatical leave at Harvard, where he won the degree of D.P.H. (1918). He was a member of several scientific societies, holding the office of vice-president of the Society of American Bacteriologists in 1915.

While still an undergraduate he became interested in bacteriological research, his first paper (in *Zentralblatt für Bakteriologie*) on the "Rise and Fall of Bacteria in Cheddar Cheese," dating from 1897. Thus began a career of scientific production which continued uninterruptedly for nearly forty years, to be terminated only at his death.

Upon his graduation in 1896 he was married to Jacquette Lee, of Rush City, Minnesota. Later in the summer his scientific talents were recognized by an appointment as director of research in the Agricultural Experiment Station, Geneva, New York. In the fall he returned to the University of Wisconsin for special study in preparation for his new responsibility. Then occurred an event which was destined to change the course of his life and give direction to a substantial part of his future research, for he was stricken with tuberculosis.

He went at once to New Mexico, where he regained his health, was appointed assistant professor of biology at the University of New Mexico (1897), professor of biology and chemistry (1900) and also acted as director of the Hadley Climatological Laboratory. Here he remained for nine years and engaged actively in varied investigations suggested by his environment. Typical of his publications at this period are: "The Effects of High Altitude on the Blood" and "Bacterial Flora of the Semi-desert Region of New Mexico." Here also he began his work on tuberculosis, which remained a major interest with him through the rest of his life.

In 1907 he was called to the University of Washington as assistant professor of bacteriology, was promoted to associate professor in 1909 and to professor in 1912. Here he published numerous papers in the pure science of bacteriology. He also made extensive studies in the field of his early interest, the bacteriology of foods, especially milk, meat and canned foods. When in 1924, by a gift of \$100,000, the McDermott Foundation for tuberculosis research was created at the University of Washington, it seemed peculiarly appropriate that Dr. Weinzirl should be made its director. This endowment gave him more freedom for research and he, together with his collaborators, began those fundamental studies on the biology of the tubercle bacillus and the desensitization of tuberculous guinea pigs which occupied his chief attention until the end.

His scientific work must be appraised elsewhere. But it may be noted that his published papers, comprising some 45 titles, are distributed about equally among three fields: (a) the pure science of bacteriology, (b) the applied field of sanitary bacteriology and public health and (c) tuberculosis.

Professor Weinzirl was a gifted teacher whose friendly counsel and sympathetic encouragement are remembered by many a grateful student. While carrying a full teaching load, he still found time for public service, holding at the time of his death the positions of secretary of the State Tuberculosis Association, member of the State Board of Examiners for Basic Science and chairman of the Public Health Committee as technical adviser of the State Planning Council. Many of his papers on sanitary bacteriology really belong to the domain of his public service. But perhaps the most valuable contribution under this category is the course which he instituted at the university for the training of laboratory technicians in bacteriology, a work in which he was signally successful and in which he took a justifiable pride.

On the personal side Dr. Weinzirl was a man of beautiful character, sincere, genuine, unselfish. His genial and kindly spirit endeared him alike to his students and colleagues, who mourn him as a friend. By his death the university has lost a painstaking investigator and sound scholar and the state a most useful and devoted public servant.

R. M. WINGER

#### RECENT DEATHS

DR. BENJAMIN LINCOLN ROBINSON, emeritus professor of systematic botany at Harvard University and emeritus curator of the Gray Herbarium, died on July 27. He was seventy years old. Dr. Robinson had filled the Asa Gray professorship since 1900; he became assistant director of the Gray Herbarium in 1890 and curator in 1892.

ELBERT W. ROCKWOOD, professor of chemistry, formerly head of the department of chemistry at the University of Iowa, died on July 17 at the age of seventy-five years.

DR. JAMES M. VAN HOOK, professor of botany at Indiana University, died on June 21. He was sixty-five years of age.

DR. LEWIS FUSSELL, a member of the faculty of Swarthmore College for nearly thirty years and professor of electrical engineering since 1920, died suddenly on July 15 at the age of fifty-three years.

DR. HENRY ROBBINS BARROWS, associate professor of education at the New York University School of Education and author of text-books on biology, died on July 16. He was fifty-five years old.

THE death on July 15 at the age of eighty-nine years is announced of John Joy Edson, treasurer of the National Geographic Society for the last thirty-four years.

DR. JOHN JENKS THOMAS, emeritus professor of neurology at Tufts College Medical School, died on July 17 at the age of seventy-four years.

DR. GEORGE MILTON LINTHICUM, professor of colonic diseases at the University of Maryland, died on July 18 at the age of sixty-four years.

WILLIAM MULHOLLAND, chief engineer of the Los Angeles Water Board, known for his construction of the Owens River-Los Angeles Aqueduct and the water system the city built in the last twenty-five years, died on July 22. He was seventy-nine years old.

JAMES McEVoy, geologist and mining engineer, died on July 19. He was seventy-three years old. Mr. McEvoy was for several years on the staff of the Geological Survey of Canada and was later geologist for the Crows' Nest Pass Coal Company at Fernie, B. C.

PROFESSOR FRIEDRICH AUGUST FERDINAND WENT, professor of botany at the University of Utrecht, died on July 26. He was seventy-two years old.

DR. ALEXANDRE GUÉNIOT, of the French Academy of Medicine, died in Paris on July 16 in his one hundred and third year. He was elected to the Academy of Medicine in 1862. His one hundredth birthday in 1932 was observed with special ceremonies by the academy, and last November all academicians rose when he attended on his one hundred and second birthday.

## SCIENTIFIC EVENTS

### THE LONDON MUSEUM OF PRACTICAL GEOLOGY

THE new Museum of Practical Geology in Exhibition Road, South Kensington, London, was opened by the Duke of York on July 3 on the occasion of the centenary of the Geological Survey of Great Britain. The Duke was received by Mr. Ormsby-Gore, first commissioner of works, and Lord Rutherford, chairman of the Advisory Council, Department of Scientific and Industrial Research.

Mr. Ormsby-Gore said that the Geological Survey of Great Britain was the oldest national geological survey in the world. It was instituted for the purpose of preparing copies of the Ordnance Survey maps geologically colored so as to be of service to science and industry by providing an accurate representation of the geology of Great Britain. The Museum of Practical Geology had developed out of the collection by the survey of specimens of rocks, minerals and fossils, and was first opened to the public in 1841. It was soon found that the importance of the collection warranted the erection of a building designed to display the work of the survey and the application of geology to the arts and industry, and in the year of the Great Exhibition the building in Jermyn Street was opened by the Prince Consort.

During the period of more than 80 years' occupation of the old building the museum had expanded and become cramped by limitation of space. The structural condition of the building deteriorated, until in 1928 the Royal Commission on National Museums and Galleries described the condition as "quite deplorable and indeed dangerous." The new building was commenced in 1929 and was substantially completed in 1933, when it was required for the World Monetary and Economic Conference. The cost of the building

was some £220,000, and a lease of the Crown site of the old premises had been granted at a rent which considerably exceeded the interest on the capital sum expended on the new building.

The arrangement of the museum was in accordance with the best modern museum practice. The gallery or exhibition space, on three floors, had been treated with simplicity of form and finish in order that the interest of visitors might be concentrated on the exhibits. The maximum intensity of natural light had been secured and special consideration had been given to the provision of the most modern forms of artificial lighting. A top floor would be devoted solely to research by the staff of the survey and by students. The building had been designed by an architect on the staff of the Office of Works, Mr. J. H. Markham. The Duke of York made the dedicatory speech.

### THE MINNEAPOLIS MEETING OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

THE council of the American Association for the Advancement of Science at the recent Minneapolis meeting, a full account of which was given in the last issue of SCIENCE, adopted the following minute:

At the close of the third Minneapolis meeting of the American Association for the Advancement of Science, which is the ninety-sixth meeting of the association, the Council of the Association desires to acknowledge and place on record its indebtedness to the many institutions, organizations, groups and individuals that have aided so effectively in promoting the success of this meeting. Among these are: the regents, the president, the faculties and departments of the University of Minnesota; the Mayo Foundation and the Mayo Clinic, at Rochester; the Minnesota State Medical Association; the local committee

for this meeting and its associates, the officers and committees of the American Association and its associated societies; the Minneapolis Civic and Commerce Association; the press of Minneapolis and the various national press associations; and the general public of the City of Minneapolis.

President Coffman and Mrs. Coffman welcomed the men and women of science and their guests at a reception Tuesday evening in the splendid Northrop Auditorium. The evening general sessions, held in the Northrop Auditorium, were well attended, as were the many scientific and business sessions held in lecture rooms and laboratories at the university and at the Mayo Clinic in Rochester. The Association is highly appreciative of the fine facilities of the University and of the Mayo Clinic, which were made available for this meeting. The symposium on Conservation, which was jointly sponsored by the University of Minnesota and the Association, was an outstanding feature of the week's program; without the aid of the University that symposium could not have been arranged. The chairman of the local committee, Dr. D. E. Minnich, and his associates were tireless in caring for the many details of the preparations for this Minneapolis meeting. Arrangements for the fine cooperation of the Minnesota State Medical Association, which met with the A. A. A. S. on this occasion, were due to Dr. E. A. Meyerding and his associates. To the Minneapolis Civic and Commerce Association and the secretary of its convention department, Mr. W. C. Walsh, the American Association and its associated societies are greatly indebted for valuable support and aid in making the meeting a success. Members of the local Press and local radio organizations were exceptionally effective in bringing the programs to the attention of the public and in arousing a pronounced general interest. Several national press associations cooperated cordially by sending out many accounts of scientific contributions that were presented at the many sessions. The local committee and officers of sections of the American Association for the Advancement of Science and of associated societies arranged many enjoyable and profitable field trips into the neighboring region, trips that constituted an important part of this summer meeting.

#### CAMP CONFERENCE FOR BOYS BY THE STEVENS INSTITUTE OF TECHNOLOGY

THE fifth annual Camp Conference of the Stevens Institute of Technology for the vocational and collegiate guidance of boys of high-school age will be held at the Stevens Engineering Camp, Johnsonburg, New Jersey, from August 18 to August 31, inclusive.

Educators and engineers, including members of the faculties of six schools and colleges, will comprise the staff. The conference is planned to help the boys to decide, first, if they should go to college; second, in what type of college each is most likely to succeed, and third, for what kind of life work or profession he is best fitted.

The program includes a series of nineteen lectures

on engineering and the relation of the Engineering College to the Liberal Arts College; comprehensive psychological and aptitude tests given under the direction of Dr. Walter Van Dyke Bingham, director of the Personnel Research Federation and professor of psychology at Stevens, and Professor Johnson O'Connor, of Stevens. From three to four hours each day are devoted to field work in surveying in charge of Professor David L. Snader, professor of civil engineering at Stevens Institute.

Dr. Harvey N. Davis, president of Stevens Institute of Technology, has announced the schedule of visiting lecturers for the camp conference. Among those who will address the conference are: Joseph W. Barker, dean of the School of Engineering, Columbia University; Dexter S. Kimball, dean of the College of Engineering, Cornell University; Bruce M. Bigelow, director of admissions, Brown University; Charles H. Breed, head master of Blair Academy. A general survey of the work of engineering will be made in addresses by: John Johnson, director of research, United States Steel Corporation; Robert Ridgway, consulting engineer to the Port Authority on the Midtown Vehicular Tunnel; William H. Taylor, president of the Philadelphia Electric Company; R. F. Gagg, assistant chief engineer, Wright Aeronautical Corporation; A. R. Stevenson, assistant to the vice-president, General Electric Company; Roy V. Wright, past-president of the American Society of Mechanical Engineers, and others. The enrolment of the past four years, Dr. Davis said, has been 159 students, representing 52 private schools and 65 high schools.

#### PROMOTIONS AT THE UNIVERSITY OF CALIFORNIA

FORTY members of the faculty of the University of California at Berkeley and at Los Angeles will resume active duty in the autumn with higher academic rank or additional titles. Eight men have been raised to the rank of professor.

At Berkeley among the sciences the following promotions have been made: C. D. Shane from associate professor of astronomy to professor of astrophysics; J. B. deC. Saunders, assistant to associate professor of anatomy; T. D. Stewart, associate to full professor of chemistry; Barbara N. Armstrong, associate to full professor of law; J. B. Leighly, assistant to associate professor of geography; H. M. Jeffers, assistant to associate astronomer at Lick Observatory; H. L. Mason, instructor to assistant professor of botany; C. B. Morrey, Jr., instructor to assistant professor of mathematics.

At Los Angeles the following promotions were made: J. Kaplan, assistant to associate professor of physics; C. M. Zierer, assistant to associate professor

of geography; A. H. Warner, instructor to assistant professor of physics.

In the College of Agriculture the following promotions were made: P. L. Hibbard, associate chemist to chemist; H. R. Guibert, assistant to associate animal husbandman; A. J. Winkler, associate viticulturist to viticulturist; P. M. Barr, assistant to associate professor of forestry; W. M. Hoskins, assistant professor and assistant entomologist to associate professor and associate entomologist; T. E. Rawlins, assistant professor and assistant plant pathologist to associate professor and associate plant pathologist; F. N. Briggs, assistant to associate agronomist; S. H. Cameron, assistant to associate plant physiologist; E. C. Voorhies, associate to full professor of agricultural economics; F. J. Veihmeyer, associate to full professor of irrigation investigations and practice; M. Kleiber, associate animal husbandman, additional title of associate professor of animal husbandry; H. J. Almquist, instructor and junior poultry husbandman to assistant professor and assistant poultry husbandman; D. E. Bliss, junior to assistant plant pathologist.

#### NOTES FROM THE CONNECTICUT AGRICULTURAL EXPERIMENT STATION

WILLIAM L. SLATE, director of the Agricultural Experiment Station at New Haven, Conn., has been appointed chairman of the State Planning Board by Governor Wilbur L. Cross. The Planning Board was given legal status by the recent General Assembly. For the past year it had functioned in an advisory capacity, as the Governor's Planning Board, carrying on research under the chairmanship of Director Slate.

Dr. Donald F. Jones, head of the department of genetics at the Agricultural Experiment Station at New Haven, has been granted leave of absence beginning on September 1. He will carry on special

research at the California Institute of Technology, Pasadena. Dr. Jones is president of the American Genetics Society.

Director William L. Slate and Dr. M. F. Morgan, of the Agricultural Experiment Station at New Haven, will attend the International Congress of Soil Science, meeting at Oxford, England, from July 30 to August 7. Dr. Morgan will read two papers based on the experimental work he has carried on at the station. The first, on the simultaneous estimation of active chemical factors in plant nutrition through tests of sodium acetate-acetic acid soil extract, is the background for Dr. Morgan's simplified method of soil testing, described in Station Bulletin 372, now on the press. In the second, Dr. Morgan will talk about changes in exchangeable bases in soils as related to fertilizer application, leaching and crop removal. This paper is based on the results of lysimeter investigations made at the substation at Windsor in which he has studied the effects of nitrogen-carrying fertilizers on different types of soil.

Besides attending the conference, Director Slate and Dr. Morgan will hold conferences with Dr. L. Dudley Stamp, director of the Land Use Survey of Great Britain. The Connecticut Stations at New Haven and at Storrs have been engaged in a somewhat similar project for several years. Because of Connecticut's vital interest in the Dutch elm disease, the director also plans to spend some time investigating control in European countries where the disease is wide-spread.

Dr. George P. Clinton, head of the department of botany at the New Haven Experiment Station, will attend the sixth International Botanical Congress to be held at Amsterdam, the Netherlands, early in September. During his European trip, Dr. Clinton will make special inquiries about the Dutch elm disease in England, Holland and in other European countries.

#### SCIENTIFIC NOTES AND NEWS

DR. MARSHALL A. HOWE, assistant director of the New York Botanical Garden for the past twelve years, a member of the scientific staff for thirty-four years, has been appointed director. He succeeds Dr. Elmer D. Merrill, who has resigned to assume the newly created post of director of the eight botanical units of Harvard University.

DR. HENRY B. WARD returned to the University of Nebraska for a homecoming celebration of the department of zoology which he founded in 1893 upon the invitation of the then Chancellor James H. Canfield. He was given a departmental breakfast by Professor D. D. Whitney, present head of the department, and an evening reception by Dean Lyman, one of his

former students. At the commencement on June 10 the degree of doctor of laws was conferred on him.

At the closing session on July 17 of the International Astronomical Union, Dr. Ernest Esclangon, director of the Paris and Meudon Observatories and professor of astronomy at the University of Paris, was elected president for the next three years, succeeding Dr. Frank Schlesinger, director of the Yale Observatory. Dr. W. S. Adams, of the Mount Wilson Observatory; Harold Spencer Jones, Astronomer Royal of Great Britain, and Dr. Hilding Bergstrand, of Sweden, were elected vice-presidents. The union accepted the invitation of the Swedish government to meet in Stockholm in 1938.

SIR CHARLES SHERRINGTON, since 1913 Waynflete professor of physiology at the University of Oxford, has retired. He has been appointed Gifford lecturer for the years 1936-37 and 1937-38.

AT the commencement exercises of the University of California at Los Angeles the degree of doctor of laws was conferred upon Dr. Robert Grant Aitken, director of the Lick Observatory, who has since retired.

DEAN E. J. McCARTLAND has retired as dean of the faculty of engineering of the University of Missouri after serving for twenty-one years. He is succeeded by Professor F. Ellis Johnson, head of the department of electrical engineering of the Iowa State College.

DR. CHARLES H. MAYO, of the Mayo Foundation of the University of Minnesota, observed his seventieth birthday on July 19.

DR. BERNARD SMITH has been appointed director of the British Geological Survey and Geological Museum as from October 1, on the retirement from that office of Sir John Flett, who has been director since 1920. Dr. Smith became geologist to the survey in 1906, and was made assistant to the director in England in 1931. The new Geological Museum in South Kensington was opened by the Duke of York on July 3.

THE doctorate of laws of Trinity College at Hartford, Conn., was conferred at commencement on Francis P. Garvan, president of the American Chemical Foundation.

THE degree of doctor of science has been conferred by the University of Cambridge on Dr. Leslie Harris, director of the Nutritional Laboratory of the university.

THE University of St. Andrews has conferred the honorary doctorate of laws on Dr. J. Hutchinson, of the herbarium of the Royal Botanical Gardens at Kew, England.

DR. RICHARD ANSCHÜTZ, professor of chemistry in the University of Bonn, has been elected a foreign honorary fellow of the Royal Society of Edinburgh.

THE Imperial College of Science and Technology, London, has elected to fellowship Professor Alfred Fowler, formerly Yarrow professor of the Royal Society and emeritus professor of astrophysics at the college.

THE *British Medical Journal* reports that at a special meeting of fellows of the Royal Society of Medicine on May 21, five new honorary fellows were elected. These were: Sir St. Clair Thomson, who was president of the society in 1924-25; Dr. Sigmund Freud, of Vienna; Dr. Joseph Jadassohn, of Zurich; Dr. George

R. Minot, of Harvard University, and Dr. R. F. J. Pfeiffer, of Breslau.

IN the department of physics of the University of Michigan, Dr. D. M. Dennison has been promoted from an associate professorship to a professorship, and Dr. W. W. Sleator and Dr. Otto Laporte have been promoted from assistant professorships to associate professorships.

DR. C. B. AIKEN, of the Bell Telephone Laboratories, New York, has been appointed associate professor of electrical engineering in charge of the department of communication engineering at Purdue University. Under Dr. Aiken's direction, the department will be completely reorganized in order to strengthen the undergraduate courses and introduce several graduate courses.

DR. FRANK H. KRUSEN, associate dean of Temple University School of Medicine, has resigned to take charge of the department of physical therapy at the Mayo Clinic, Rochester, Minn. Dr. Krusen has been director of the department of physical medicine at Temple University Hospital since 1931.

DR. MILTON S. PLESSET, who for the past two years has been studying with Professor Niels Bohr at Copenhagen, has been appointed instructor in physics at the University of Rochester.

DR. ROBERT F. BACHER has been appointed instructor in physics at Cornell University and will begin his work there in September. After receiving the Ph.D. degree from the University of Michigan, Dr. Bacher spent one year each as National Research fellow at the California Institute of Technology and at the Massachusetts Institute of Technology. Recently he has been instructor in physics at Columbia University.

HOWARD A. SMITH, until recently a National Research Fellow at the Metals Research Laboratory of the Carnegie Institute of Technology, is now a research associate at the Massachusetts Institute of Technology. With another associate, he is investigating fundamental causes for the corrosion of stainless steels in the interests of the Chemical Foundation. This work is being guided by a faculty committee of which R. S. Williams is chairman.

ROBERT C. STAUFFER, A.B., Dartmouth, 1934, a graduate student at the University of Minnesota, has been appointed an instructor in biology at Dartmouth College. Mr. Stauffer will spend the latter part of the summer at Woods Hole, going to Dartmouth in September.

THE title of professor of statistics has been conferred by the University of London on Dr. E. S. Pear-

son, in respect of the post held by him at University College.

DR. ORESTES H. CALDWELL, electrical engineer, has been named science director of the Hall of Science of the National Electrical and Radio Exposition, to be held at the Grand Central Palace from September 18 to 28.

THE Dutch and French Governments have officially recognized the International Office for the Protection of Nature and have appointed the following delegates to be their representatives to the general council of the office: *Delegates for Netherlands and Dutch East Indies*: Dr. P. G. van Tienhoven, president of the Society for Nature Protection in Netherlands; Dr. W. A. J. M. van Waterschoot van der Gracht, chief engineer of Mines; Professor Dr. L. Ph. le Cosquino de Bussy, director of the Colonial Institute, Amsterdam; Dr. J. C. Koningsberger, former Minister of Colonies. *Delegates for France and Colonies*: M. Bolle, conservator of forests, Ministry of Agriculture, Paris; Professor Dr. A. Gruvel, general secretary of the National Committee for the Preservation of Fauna and Flora in the Colonies; Raoul de Clermont, president of the Section for Nature Protection of the Société Nationale d'Acclimatation de France.

*Nature* reports that Dr. R. F. Lawrence, who has been assistant in charge of reptiles, amphibians and arachnids at the South African Museum since 1922, has been appointed director of the Natal Museum, Pietermaritzburg.

THE Secretary of the Interior has appointed as executive secretary of the Division of Geographic Names Dr. George Curtis Martin, of Corvallis, Oregon, who was for twenty years a geologist with the U. S. Geological Survey. The Division of Geographic Names, successor to the U. S. Geographic Board, was set up by Secretary Ikes under the authority of President Roosevelt's Executive Order of April 17, 1934.

DR. OSCAR RIDDLE, of the Carnegie Institution of Washington, sailed on July 20 for Europe where he will present a paper "On Anterior Pituitary Hormones" before the fifteenth International Physiological Congress at Leningrad and Moscow, which meets from August 9 to 17. While abroad he will visit various physiological laboratories in England,

Denmark, Russia, Jugoslavia, Germany, Holland and France.

DR. HOWARD DITTRICK, of the School of Medicine of Western Reserve University, has been appointed official delegate of the United States Government to the tenth International Congress on the History of Medicine, to be held in Madrid, Spain, from September 23 to 29. Dr. Dittrick has also been appointed delegate of the American Association of the History of Medicine.

SIR HUBERT WILKINS arrived in the United States from Europe on July 24 *en route* to South America to join an expedition of the National Geographic Society to the Antarctic. After his return next March he expects to begin preparations for his second under-sea exploration of the North Polar seas.

AT the close of the initial program presented by west coast geographers in connection with the meetings of the Pacific Division of the American Association for the Advancement of Science, held at the University of California at Los Angeles during the last week of June, the formal organization of an Association of Pacific Coast Geographers was completed. Dr. Otis W. Freeman, of the Washington State Normal School at Cheney, was elected *president*; George C. Kimber, of the Sacramento Junior College, *vice-president*, and Willis B. Merriam, of the University of Washington, *secretary-treasurer*. The meeting in 1936 will be held in conjunction with the regular meetings of the Pacific Division in Seattle under the auspices of the University of Washington.

AT a meeting on July 26 of Arctic explorers at the American Museum of Natural History steps were taken to organize the American Polar Society, which will issue semi-annually as the organ of the society *The Polar Times*. The first number of the magazine has recently appeared. The society has an initial roll of eighty-four members living in eighteen states and in England, France, Norway, Germany, Turkey and Cuba. Its chief object is to compile data relating to the polar regions in cooperation with the Scott Polar Research Institute in Cambridge, England, the New Zealand Antarctic Society, the Arctic Institute at Leningrad and similar groups throughout the world.

## DISCUSSION

### THE NEW ERGOT ALKALOID

PERHAPS I ought not to intervene in a discussion in which I am not directly concerned; but, apart from the fact that I have been engaged in research on the

pharmacology of ergot, and side issues therefrom, for over 30 years, I have been in close touch with Dudley and Moir's work from the very beginning. When Moir, in June, 1932, published the observations which

formed the real starting point of all the new development, he kindly allowed me to add a note, in which I recorded my conviction that his method had revealed an ergot principle then unknown, and stated explicitly that Dudley had already joined Moir in the search for it.

The really serious aspect of the position which has now arisen is the threatened confusion in the literature. For alkaloids which I believe to be all identical with that which Dudley and Moir first clearly described and named Ergometrine, three other names have already been put forward, *viz.*, Ergotoein (Kharasch and Legault), Ergobasine (Stoll) and now Ergostetrine (Thompson). What is to be done to get a decision, among these rival claimants, as to the name to be adopted into the scientific literature, and into the national Pharmacopoeias, as the proper name of this alkaloid, if only one is really in question? We seem to need an expert and impartial judge or court to decide the matter. I do not expect that I should be accepted in that rôle. The best that I could hope to do would be to hold a brief—an easy one, it seems to me—for ergometrine, and to present the case for it, with an effort to be fair and courteous. I should like to acknowledge on behalf of my colleagues, and to reciprocate, Thompson's graceful recognition of their success in that respect.

One could hardly expect our judge, in such a case, to accept the invidious responsibility of allowing an appropriate handicap to the men who first started the investigation, as against those who took the risk of rival attempts to anticipate its completion. He would have to base his decision solely on priority of publication and proof of identity or difference; and I should be content to plead on those lines. I should ask the court to assent to certain principles, by which such a matter could be decided.

(1) Speculative argument should be inadmissible on the question of identity. Stoll bases his whole argument for "Ergobasine" on the suggestion that his alkaloid is *not* identical with Ergometrine, making an entirely courteous acknowledgment of Dudley and Moir's priority in discovering and describing the latter. One of the claims of Kharasch and Legault for "Ergotoein" is also based on the suggestion that it is a different alkaloid. I do not honestly believe that the evidence is sound in either case; but argument on such a matter is out of place. The recognized method of decision is by an exchange of specimens, or their submission to a neutral umpire, if that is preferred. In any case, while no method is yet available for the preparation of any of its rivals, Dudley<sup>1</sup> has published a simple method, by which any competent chem-

ist can prepare and purify Ergometrine for himself. The onus of proof, I should suggest, is thereby laid on any one else who claims that his alkaloid is a different chemical substance, and therefore entitled to a different name.

(2) I should ask the court to rule against any attempt to obtain a spurious priority, by transferring a name from one kind of substance to another. If A, for example, had described a preparation, emphasizing as its chemical characteristics that it was non-alkaloidal and probably related to the pituitary oxytocic principle, and had applied a name to it; and if B, very shortly afterwards, had described the isolation of an alkaloid and given a careful preliminary description of its characters; then I should urge that A had no right subsequently to apply his name to B's alkaloid, and that neither that procedure nor the omission of any reference to B would support A's claim to priority in its discovery.

(3) I should urge that, when once a substance, such as an alkaloid, has been obtained practically pure and properly described, so that it can be recognized by a competent chemist, the fact that somebody else obtains enough of it for further recrystallization, and thereby raises its melting point by a few degrees, does not entitle him to rename it. If this practice were admitted, every alkaloid that has ever been discovered might soon require a separate catalogue for its nomenclature.

I should ask the court to rule, then, that, if the names Ergometrine and Ergotoein had been applied to the same alkaloid, Ergotoein was inadmissible under (2) and (3); and that if, under (1), it was claimed that Ergotoein or Ergobasine had been applied to a different alkaloid, its sponsor should bring proof of its different identity.

(4) I should ask the court to rule out, as not evidence, a suggestion that its sponsors had "succeeded in separating Ergotoein from the known ergot alkaloids late in 1933" (1923 being, of course, a misprint). Dudley and Moir might, with equal truth but equal irrelevance, claim that they had separated Ergometrine from the known ergot alkaloids already in 1932. What is on *published* record is that Ergotoein was still the name of a supposedly non-alkaloidal preparation early in 1935, and for a month after Dudley and Moir had published their paper.

My real difficulty, in asking for the application of such principles as the above, would arise in dealing with Thompson's claim for the name "Ergostetrine." The friendly and reasonable form of his statement (SCIENCE, June 28, 1935) and his frank recognition of the difficulties created by his method of publication, make me reluctant to be critical. I believe that he will understand me, however, if I say that the difficulties

<sup>1</sup> Pharm. Jour. (iv), 80: 709, 1935.

have not been removed. We learn now that the article which appeared in the *Journal of the American Pharmaceutical Association*, in March, 1935, formed part of a thesis submitted at Baltimore in May, 1934. I should leave the court to decide whether deposition of a thesis in university archives constitutes "publication," with reference to the point under discussion; but, whatever the decision, the difficulties would remain. It is admitted that the name "Ergostetrine" appeared neither in the thesis nor in the article published ten months later. Thompson tells us that he did not name the alkaloid, although he had it crystalline, because he was doubtful as to whether it might not be Küssner's "Ergoclavine"; but he does not explain why the fact that a crystalline alkaloid had been obtained still remained in a footnote in the article published in May, 1935; or why no details of its properties were even then given, which would have excluded the possibility of its being, indeed, Ergoclavine. Thompson gives, indeed, in his statement in SCIENCE of June 28, an account of his communication in April, 1935, to the American Society for Pharmacology, etc., containing physical data sufficient to make probable the identity of his alkaloid with ergometrine; yet in the *Journal of Pharmacology* for June, 1935, in the official abstract of this same communication by Thompson, there is no reference to any such identifying data or to the fact that anything had been crystallized, or to the name "Ergostetrine." The reference there is still to "X-alkaloid," as in the article in the *Journal of the American Pharmaceutical Association* for May, 1935, where, as Dudley and Moir have observed, apart from the footnote merely mentioning the crystallization of something, there is no evidence as to the nature of "Alkaloid-X," except physiological evidence that it still contained much alkaloid of the Ergotoxine type.

What are we to make of all this? Honestly I do not know, and can only await further information. It can be taken for granted that Dudley and Moir would not wish to deprive Thompson, or any one else, of any priority which would properly be awarded to him by my imaginary judge, on full evidence, such as is not available to us. Thompson's article in SCIENCE of June 28 contains the first public reference which we have seen to the name Ergostetrine, or to any data in Thompson's possession to support a claim that he had prepared an alkaloid identical with Ergometrine.

The important matter for early decision—and it is really urgent—is that of the proper name for scientific application to the new alkaloid, which we probably all believe to be one and the same, whatever some may for tactical purposes have suggested. It is really important that scientific journals and still more important that Pharmacopoeias should adopt one com-

mon name. For the former it is desirable, and for the latter it is essential, that the name should be free from protection by trademark. There is a hint in Thompson's statement that his difficulty in presenting his observations and his suggested nomenclature in the normal course of scientific publication may have been in some way connected with patent and trademark applications. I may be mistaken and should be glad to find myself so. My views on patents by academic workers and their effect on the proper spirit of scientific cooperation are well known to my friends, and I need not enlarge upon them here. What I wish to plead, as my fifth and last submission to the court, is:

(5) That if an investigator protects by trademark or patent a name which he desires to apply to a new substance, he ought to lose any claim to the acceptance of that name for general scientific use. As Thompson realizes, there is no published record of the properties of what he had really in hand, when he "legally assigned" the name Ergostetrine to it in May, 1934. A system, by which a name could be registered and protected, without mention in the literature, and held ready for scientific application to a substance when somebody else had published its isolation and its properties, is obviously unacceptable in principle, whatever may be the true facts in this case. And the surrender of a trade monopoly in the name, to facilitate this maneuver, would not render it more acceptable.

As at present advised, therefore, I should still ask the scientific court to hold that Ergometrine, as the first name openly applied in scientific publication to the new alkaloid, by those who first described its isolation and its characters, without any kind of restriction by patent or trademark, ought to be recognized as the neutral, scientific name. And I should be content to accept the decision of the court, if it were composed of the many American friends whose standards I know and trust.

H. H. DALE

THE NATIONAL INSTITUTE  
FOR MEDICAL RESEARCH  
HAMPSTEAD, LONDON  
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#### SHALL THE DEPARTMENT OF THE INTERIOR BECOME THE DEPARTMENT OF CONSERVATION AND WORKS?

DURING the fall of 1934, it became evident that the administration of the Taylor Grazing Act on the public domain by the Department of the Interior was being used as a pretext to bring pressure to bear upon President Roosevelt to use his authority (which expired March 15, 1935) to transfer the National Forests to that department.

As the result of a nation-wide protest against such

a measure, the Secretary of Agriculture, following a definite drive instituted by Mr. Ickes at the American Game Conference in New York, in December, stated that he was authorized to announce that no such move was contemplated.

This effort having failed, as did the previous attempts of Secretaries Lane, Fall, Works, Wilbur and Ickes, the plan was hit upon to renew the presidential authority for the reorganization and transfer of departments, but gently to guide his hand in the proper direction. The name of the Department of the Interior was to be changed to that of Conservation and Works. The President would then be authorized to transfer to this department any commission, board, bureau division or service engaged in conserving the national resources (or in carrying on public works activities) in the United States or its territories or possessions; and he could also transfer from the Department of the Interior to other departments any such body *not engaged* in conserving the natural resources.

This bill was introduced into the Senate and House, before the committees on expenditures in executive departments, as S-2665 and HR-7712 accompanied by statements prepared by Secretary Ickes giving evidence to show that the Department of the Interior was in effect the center of conservation activities, listing the agencies within his department so employed and the measures and their character which had originated there. All references to the conservation work of the Department of Agriculture were omitted.

During the hearings and in correspondence the Secretary of the Interior endeavored to suppress critics of this measure, and declined to commit himself as to the purposes of the bill or the agencies whose transfer was contemplated. The Forest Service and the Society of American Foresters were charged by him with maintaining a strong and efficient lobby, from which alone arose opposition to the measure. The Senate Committee on Public Lands, to whom the measure was referred, reported it out favorably. At the time of writing, the Committee on Expenditures of the House had not reported.

The Department of the Interior officials realize that grazing regulation on the public domain will be constantly compared with that on the National Forests, under the Department of Agriculture, and that as a matter of sound administration, the two branches should be in the same department. Unwilling to take any chances on an executive decision to transfer this grazing branch to agriculture, as was done with soil erosion, this bill is intended to make the transfer mandatory in the direction desired, taking with it, lock, stock and barrel, the forests, the wild life and the watersheds, and cleaving the work of forestry in two. Farm

forestry and extension, cooperative fire protection, the combating of forest insects and diseases, and all the research and educational work would remain logically with the Department of Agriculture; thus a Forest Service would then exist in both departments. This article is not a discussion of the reasons why such legislation should not pass, which would occupy more space than is available. They hinge on two points. First, the organic resources, soil, forests and wild life, constitute a balanced whole, which can be regulated intelligently only by unified control in the hands of men trained in the fundamentals of biology and administration of such problems. Second, the continuous and continuing record of the Department of the Interior is such as to prevent those who understand these problems from extending their confidence to this department as the custodian of such resources.

H. H. CHAPMAN

YALE UNIVERSITY

#### A TERMINOLOGY PROPOSED FOR MOTION PICTURE FILMS

THE possibility of taking motion pictures at a known speed and then projecting the processed film at the same or at a different rate of speed permits control of the time variable for analytical purposes. This is one of the very few methods available for the alteration of time and is of fundamental importance to many branches of science. The motion picture technique has been used for a half century,<sup>1</sup> but as yet there is no consistent terminology.

When the film is taken at a slow rate over a period of time and then projected at a more rapid rate the action is reviewed in a few minutes, even though the original action took hours. Such films have been called stop motion, time lapse, accelerated motion, etc. These terms are inconsistent and confusing. During the early development of motion pictures Pizon<sup>2</sup> used the term "biotachygraphic" for his films of this type, meaning to write life rapidly. While the term "tachygraphic" has been used<sup>3</sup> this is not the best name because it also means shorthand. To see a process in less time is a sort of shorthand, but the combining terms for the other three types of motion picture film are not satisfactory. The best word to describe this kind of film seems to be "tachykinetic," and this is proposed for future use to describe a motion picture film that is projected on the screen at a faster rate than the film was taken in the camera.

If a motion picture is projected at the same rate as it was taken no change in time-rate occurs, and

<sup>1</sup> O. W. Richards, *Jour. Biol. Photog. Assoc.*, 1933, 2: 39-55.

<sup>2</sup> A. Pizon, *Congrès Zool. Bern.*, 1904, pp. 404-409.

<sup>3</sup> O. W. Richards, *Jour. Biol. Photog. Assoc.*, 1934, 3: 64-71.

such a film should be called "isokinetic." The rate of exposure in the camera should be marked clearly on the film to avoid confusion between the 16 frames per second used for silent films and the faster rate of 24 frames per second used with sound films. The latter more rapid rate is coming into use for silent films and may become ultimately the standard rate for "isokinetic" films.

Projecting the film at a slower rate than that at which it was taken retards the rate of motion and is the familiar slow motion picture. Slow motion is sometimes confused with stop motion or lapsed time films which are opposite in kind. Consequently, to avoid any misconception the term "bradykinetic" is proposed to denote any film to be projected at a slower rate than was used in making the film.

The three types of film are fundamentally different because the ultimate speed on the screen of the process photographed has to be decided before making the film and determines the camera speed. Much more film per minute is used in making "bradykinetic" films than with "tachykinetic" films. A "bradykinetic" film can not be obtained by projecting rapidly an "isokinetic" film, except within very narrow limits, because the intervals between exposures are too long, resulting in a blurred effect.

Therefore, the three terms herein proposed distinguish different kinds of motion picture film and give a uniform terminology which precludes confusion. The only other description required is a statement of the camera and projector speeds. The ratio of these speeds shows how much, if any, the actual time relations are altered. The rates are usually constant for a given film, but they need not be constant, as varying the rates gives a new relative time that may be very useful to the investigator. The relation of this varying time to the original time can be obtained from the acceleration (or retardation) of both the camera and the projector.

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## QUOTATIONS

### THE FOREST SERVICE

ANOTHER attempt is under way to get the national forests and the forest work of the government transferred from the Agricultural Department, where the forests are safe and the work well done, back to the Department of the Interior, from which they were taken because of wretched management.

The present attempt is made under cover of an ef-

fort (Senate Bill 2665) to change the name of the Interior Department to the Department of Conservation and Public Works. The transfer of the national forests and the Forest Service is not mentioned in the bill, but is planned for later on.

Conservation is too broad a subject to be confined to any one department. Nearly all of them deal with

<sup>1</sup> Abstract.

it in one form or another. A Department of Conservation would be almost as illogical as a department of typewriting or a department of wastebaskets, which everybody has to use.

The conservation policy itself, and about every important conservation movement for the last thirty years, originated in the Department of Agriculture. It has shown practical horse sense in dealing with natural resources intelligently, uprightly and without fraud or loss.

In contrast, the record of the Interior Department is far and away the worst in Washington. Every natural resource, without exception, that has been held for disposal by the Interior Department—public lands, Indian lands, coal, oil, water power and timber—has been wasted and squandered at one time or another. It is one long story of fraud in public lands, theft in Indian lands and throwing the people's property away.

Most of the fights for conservation have been made to save natural resources belonging to the people which the Interior Department was throwing away. The national forests must not go the same road.

Secretary of the Interior Ickes is sincere and honest, but he cannot live forever. Secretary Garfield was honest, but Secretary Ballinger, his successor, tried to give away the people's water powers and the coal lands in Alaska. The resulting scandal cost Taft his reelection. And everybody remembers Teapot Dome,

when Secretary Fall handed the navy's oil lands over to the despoilers. Fall tried hard to get his hands on the national forests.

Ickes is my friend, Wallace is my friend. But the national forests could not be better handled in the Interior Department than in the Department of Agriculture, where they have been safe for thirty years. What is the use of rocking the boat?

The Forest Service is completely free from politics where it is. Ickes himself is straight, but the whole history of the Interior Department is reeking with politics. The tradition of the Interior Department is to put private interests first. The tradition of the Agricultural Department is to put public interests first.

Wood is a crop. Forestry is tree farming. It belongs in the Department of Agriculture with all other farming and production from the soil.

Undoubtedly if Secretary Ickes got the national forests he would do his level best. But he has more work now than any other cabinet officer in Washington. The national forests are bigger than all the Atlantic States, from Maine to Virginia inclusive. Why put this additional load on a man who has too much to do already? Let the national forests stay where they are.—*Gifford Pinchot, former governor of Pennsylvania, forester, U. S. Department of Agriculture, 1896 to 1910, in The New York Times.*

## SCIENTIFIC APPARATUS AND LABORATORY METHODS

### CONSTRUCTION OF A CARTESIAN NOMOGRAM FOR THE LAW OF MASS ACTION

GIVEN the equations

$$(1) \quad [\text{Total A}]^* = [\text{A}] + [\text{AB}]$$

$$(2) \quad [\text{Total B}] = [\text{B}] + [\text{AB}]$$

and the mass action equation

$$(3) \quad \frac{[\text{A}] \times [\text{B}]}{[\text{AB}]} = \text{K}$$

it is often required to calculate values for  $[\text{A}]$  or  $[\text{B}]$  from values for  $[\text{Total A}]$  and  $[\text{Total B}]$ . This is most conveniently done with the aid of a Cartesian nomogram, of which the abscissas and ordinates represent  $[\text{Total A}]$  and  $[\text{Total B}]$ , respectively, and on which  $[\text{A}]$  or  $[\text{B}]$ , or both, appear as families of curves, each value for  $[\text{A}]$  or  $[\text{B}]$  being represented by a straight line.

The general equations for such a nomogram, as obtained from Equations 1 to 3, are

$$(4) \quad [\text{Total A}] = \frac{[\text{A}] \times [\text{Total B}]}{\text{K} + [\text{A}]} + [\text{A}]$$

\* The brackets [ ] indicate concentrations, in moles per liter.

$$(5) \quad [\text{Total B}] = \frac{[\text{B}] \times [\text{Total A}]}{\text{K} + [\text{B}]} + [\text{B}]$$

Construction of the nomogram from these equations offers no difficulties, but can be still further simplified.

From Equation 3, when  $[\text{A}] = [\text{AB}]$ ,  $[\text{B}] = \text{K}$ , and when  $[\text{A}] = [\text{AB}] = [\text{B}] = \text{K}$ ,  $[\text{Total A}] = [\text{Total B}] = 2 \text{ K}$ . It follows that a straight line passing through the points  $[\text{Total B}] = \text{K}$ ,  $[\text{Total A}] = 0$ , and  $[\text{Total A}] = [\text{Total B}] = 2 \text{ K}$ , represents all points at which  $[\text{A}] = [\text{AB}]$  and therefore at which  $[\text{Total A}] = 2 [\text{A}]$ . If this line is drawn the desired points for  $[\text{A}] = \frac{[\text{Total A}]}{2}$  may be located upon it and connected by straight lines with the corresponding points for  $[\text{A}] = [\text{Total A}]$ ,  $[\text{Total B}] = 0$ . Figure 1 illustrates the construction of the nomogram by this method. If desired the iso- $[\text{B}]$  lines may be located by the same method.

When the value for  $\text{K}$  is small, graphic extrapolation of the line representing the points  $[\text{Total A}] = 2 [\text{A}]$ , and of the iso- $[\text{A}]$  lines passing through points located upon it, may be inaccurate. In such a case a line further removed from the  $[\text{Total A}]$  axis, includ-

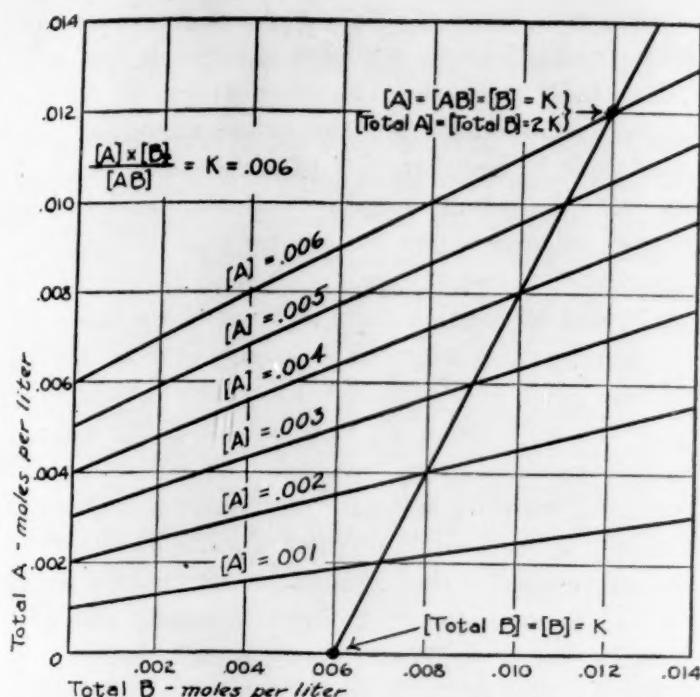


FIG. 1. Cartesian nomogram for law of mass action.

ing all points for  $[Total A] = n [A]$ , and representing all points at which  $[B] = (n-1)K$ , when  $n$  is a number chosen to give a line suitable for the purposes of graphic extrapolation, may be readily located. It follows from Equation 3 that when  $[A] = [B] = (n-1)K$ ,  $[Total A] = [Total B] = (n-1)K + (n-1)^2K$ . A line is drawn through the points  $[Total B] = (n-1)K$ ,  $[Total A] = 0$ , and  $[Total A] = [Total B] = (n-1)K + (n-1)^2K$ . The desired points for  $[A] = \frac{[Total A]}{n}$

may be located upon it and connected, by straight lines, with the corresponding points for  $[A] = [Total A]$ ,  $[Total B] = 0$ .

The method as described is, of course, applicable only to mass-action equations in which all of the components appear in the first power. A similar, but somewhat more complex nomogram, in which all necessary curves are straight lines, has proved of value in the case of mixtures of two substances when two dissociation constants are involved.

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## SEPARATION OF ONE COMPONENT OF POTATO RUGOSE MOSAIC BY pH DIFFERENCE

KOCH<sup>1</sup> showed that certain treatments inactivated one component of potato rugose mosaic without affecting another component ("mottle") which is probably identical with that called "latent mosaic" by SCHULTZ *et al.*<sup>2</sup> In the writer's experiments juice from rugose mosaic potato plants was applied mechanically to tobacco plants after its adjustment to different pH values by means of dilution with citrate or phosphate buffer solutions. With the pH 3.6 or less, no infection occurred. At a range of 4.0 to 5.5, only the latent mosaic appeared. From 5.6 to 7.6 rugose mosaic resulted and at 9.7 only the latent mosaic was transmitted. It was also found that borate ions exhibited a marked toxic effect on the components, while citrate and phosphate ions showed little difference, if any, in their specific toxicity at concentrations less than 0.1 normal. The toxicity was found to vary with the time of contact between the infectious juice and the buffer solutions.

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## A SIMPLE METHOD FOR READING FILM-STRIPS

IN a recent communication in SCIENCE<sup>1</sup> Dr. Seidell called attention to the "Biblio Film Service" maintained by the library of the U. S. Department of Agriculture, Washington, and described a magnifier, to cost in the neighborhood of \$10, for reading the film-strip. The writer recently obtained some of these film-strips and discovered that they could be read with ease under the low power of the ordinary binocular dissecting microscope. With such magnification about two thirds of the page may be brought into sharp focus, with the added advantage of being able to use both eyes in reading.

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## SPECIAL CORRESPONDENCE

### BIOLOGY OF SHELL-MOVEMENTS OF THE OYSTER

IN recent work by Nelson,<sup>1</sup> Galtsoff,<sup>2</sup> Marshall Webb<sup>3</sup> and Hopkins<sup>4</sup> on recording graphically and

<sup>1</sup> T. C. Nelson, Report N. J. Exp. Sta., U. S. A., for 1920 (1921).

<sup>2</sup> P. S. Galtsoff, Bull. Bur. Fish., U. S. A., Vol. 44, Doc. No. 1035, 1928.

continuously the opening and closing movements of oysters during one or more days, interesting observa-

<sup>3</sup> H. Marshall Webb, Jour. du Conseil, 5: 3, 1930, Copenhagen.

<sup>4</sup> A. E. Hopkins, Bull. Bur. Fish., U. S. A., 47: 1, 1931.

<sup>1</sup> Karl Lee Koch, Phytopath., 23: 319-342, 1933.

<sup>2</sup> E. S. Schultz, *et al.*, Phytopath., 24: 116-132, 1934.

<sup>1</sup> SCIENCE, February 15, 1935.

tions have been made indirectly on the biological activity of the adductor muscle components. This muscle consists, as is well known, of a large semi-translucent motor striated component and a smaller opaque so-called "catch" muscle. Graphs obtained by Galtsoff of the movements of the American oyster, *O. virginica*, are shown in Fig. 1, A. Somewhat similar figures (see

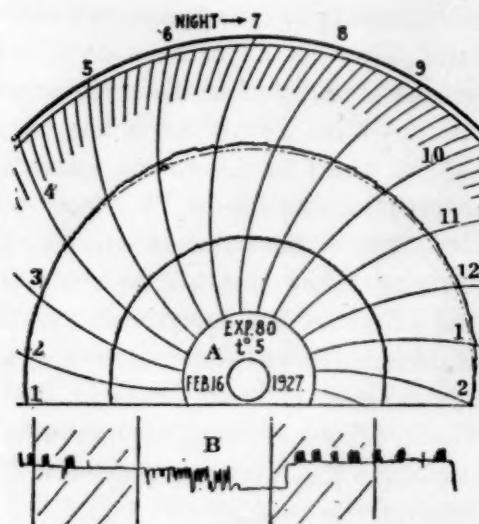


FIG. 1. A. Records by Galtsoff of shell-movements of *O. virginica*; B. Records by Marshall Webb of shell-movements of *O. edulis*.

Fig. 1, B) were obtained by Marshall Webb for the European oyster, *O. edulis*. Complete or almost complete closure is shown at infrequent intervals; this is the common natural movement when the animal closes the shell suddenly to extrude rejected food-material.<sup>5</sup> Nelson obtained his graphs from oysters actually immersed in the sea and interpreted the frequent partial closures as rejection of filtered sediment and inferred therefore that the oysters were feeding actively. Galtsoff obtained his graphs from oysters kept in glass-fronted tanks under temperatures when feeding does not occur and observed that rhythmic partial closure was not accompanied by rejection of unwanted filtrates or excreta. He suggests these partial rhythmic closures may be caused by various stimuli, *e.g.*, mechanical, changes in illumination, changes in pH, gas content, presence of certain chemicals. It seems unlikely, however, that stimuli of this kind can have operated in all the experiments. I have myself observed a quick partial closing which had the effect and no doubt the design of shaking ropes of mucus from the edge of the gill on to the mantle, but this again can hardly explain all the rhythmic partial closures obtained by Galtsoff. A more probable suggestion is that when partial closing does not occur from any other cause, it may be a relief contraction effected by the motor component to reduce fatigue in

<sup>5</sup> J. H. Orton, *Jour. Mar. Biol. Assoc.*, 9: 1, 1913, Plymouth.

the catch component of the muscle. If partial closing occurs from whatever stimulus, fatigue is probably automatically relieved. The catch muscle is usually regarded as operating in the closed condition. Its major work is, however, that of maintaining the shell in a variable but fixed open condition, since oysters are open to some extent the greater part of their life. Biologically, therefore, the function of this muscle is mainly that of position fixing. There is the objection to this suggestion regarding fatigue that so far no evidence could be obtained by either Parnas<sup>6</sup> or Bethe<sup>6</sup> of work done by the position-fixing muscle, but it is perhaps more reasonable to doubt the evidence than the work done, for some minimum quantity of energy is required throughout the life of almost all bivalves to hold the shell against the maximum opening pull of the ever-operating hinge ligament, and it is probable that in no bivalve does the shell ever gape so widely in life as in death. Anaerobic respiration occurs in certain bivalves,<sup>7</sup> the European oyster<sup>8</sup> and without doubt also in the American oyster (see 9, Table 3), so that small variations in metabolism are intrinsically difficult to detect; nevertheless, further investigations on this subject by the ingenious experimental methods used especially by American workers may be expected to yield critical information.

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FEBRUARY 23, 1935

#### ON THE SITE OF ACTION OF ACETYLCHOLINE AND ITS SIGNIFICANCE

SINCE acetylcholine is closely identified with the cholinergic agent elaborated during autonomic nerve function, its properties assume particular importance and its site of action especial significance. It has been commonly assumed, though never completely demonstrated, that acetylcholine acts directly on the peripheral tissues innervated by parasympathetic nerves.

The current assumption concerning the direct action of acetylcholine has recently been questioned by Armstrong,<sup>1</sup> who has made the interesting observation that when the embryo fundulus heart is aneural its threshold for acetylcholine is higher than physiological limits. Moreover, when functional innervation of the heart does occur, the heart then responds to minute amounts of acetylcholine. From this it was concluded

<sup>6</sup> See Bayliss, "Principles of General Physiology," p. 538, 1927.

<sup>7</sup> J. B. Collip, *Jour. Biol. Chem.*, 49: 2, 297, 1921, and bibliography.

<sup>8</sup> J. H. Orton, *Fishery Investig.*, England, II, Vol. 6, 3, p. 65, 1924.

<sup>9</sup> P. S. Galtsoff and D. V. Whipple, *Bull. Bur. Fish.*, U. S. A., Doc. No. 1094, 1931.

<sup>1</sup> P. B. Armstrong, *Journal of Physiology*, 84: 20, 1935.

that acetylcholine exerts its effect on the parasympathetic ganglia or the post-ganglionic nerves and not on the cardiac muscle itself.

Unfortunately, in the adult heart it is impossible to remove the outlying parasympathetic ganglia so that the Armstrong experiment can not be repeated with adult tissue. The mammalian eye, however, is suitable for the investigation of this question, since the parasympathetic ganglion (ciliary) can be readily removed. Engelhart<sup>2</sup> has shown that the iris in the cat contains a cholinergic substance resembling acetylcholine and that oculo-motor nerve stimulation increases the cholinergic substance within the iris. Constriction of the pupils simultaneously with an increase in cholinergic substance suggests that the two changes are related.

Hence, in an attempt to demonstrate the actual site of action of acetylcholine in the eye, the following experiments on cats were done. The ciliary ganglion was removed and subsequently identified by histological examination. In four animals immediately after the removal of the ciliary ganglion a slit was made in the margin of the cornea and some of the fluid of the anterior chamber allowed to escape. This usually caused the dilated pupil to become slightly narrower. When equilibrium had been reached a needle was inserted in the anterior chamber and 0.1 cc 1/1,000,000 solution (0.1 microgram) of acetylcholine bromide solution was injected. Constriction of the pupil occurred within 15 to 30 seconds and was complete within a minute. As a control procedure 0.1 cc of Ringer solution was injected several times. The Ringer solution and needle produced slight or no effect on the size of the pupil. These experiments demonstrate that acetylcholine is effective in the eye when directly applied to the iris in the absence of the ciliary ganglion.

To ascertain whether the constriction of the pupil was due to the action of acetylcholine on the radial muscle or the parasympathetic nerve endings the post-ganglionic parasympathetic nerve fibers were allowed to degenerate following ciliary ganglion removal in three additional cats. The pupil of the unoperated side served as a control. After 6 to 12 days the dilated pupil on the deganglionated side showed no constriction after conjunctival instillations of 1 per cent. physostigmine solution, and the above-described procedure of slitting the cornea, controlling with Ringer solution, and injecting 0.1 microgram acetylcholine into the anterior chamber of the eye, was repeated. Constriction of the pupil was again prompt and complete, except where it was partially impeded by connective tissue adhesions. After atropinization, acetylcholine no longer had any effect. In one cat the

eye was removed and the iris studied *in vitro*. Though of a similar nature, the results were less satisfactory than those of the *in vivo* experiments.

These experiments demonstrate that, at least in so far as the iris of the cat is concerned, the action of acetylcholine is peripheral to the postganglionic fibers, and presumably a direct one on the radial muscles. This is of interest in relation to the experiments of Armstrong indicating that embryonic muscle does not acquire its sensitiveness to acetylcholine until after cholinergic nerves have reached it. Generalizing from both types of experiment, it would appear that the physiological properties of the muscle (adrenergic or cholinergic) are bestowed upon it by the proximity of specific nerve fibers and that, once acquired, the specific sensitiveness is retained, at least for a time, after degeneration of the nerve fibers. Since it is probable that many smooth muscle fibers do not receive direct nerve connections, it is necessary to assume that the nerve has a sphere of influence in functional differentiation which extends beyond its terminations. This influence may be analogous to the effect of neighboring cells on structural differentiation, of which there are many examples in experimental embryology.<sup>3</sup>

These preliminary observations permit of no conclusion as to whether the response to acetylcholine is retained permanently in the absence of the parasympathetic nerve supply.

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#### PIGMENTATION IN BLACK-HAIRED RATS<sup>1</sup>

IT is a known fact that when young black rats of the hooded variety are put on a sole diet of whole milk the black hairs become gray.<sup>2</sup> However, I have observed with all-black rats that this does not occur simultaneously all over the body of the animal but in a certain sequence. At the end of the third week of the milk diet the graying of hair first becomes noticeable on the front legs (outer parts), shoulders, around the eyes and around the nose. Next the hair on the belly, the lower part of neck, around the mouth, on the inner and outer parts of all four legs begins to

<sup>1</sup> See H. Spemann and Hilde Mangold, *Arch. f. Entwickel.*, 100: 599, 1923-24; C. L. Yntema, *Journal of Experimental Zoology*, 65: 317, 1933.

<sup>2</sup> Paper Number 311 of the Miscellaneous Journal Series of the Minnesota Agricultural Experiment Station.

<sup>2</sup> Bakke (*La Medicina Italiana*, 9: 574-576, 1930) observed that hairs of black rats which were fed basal diet and his vitamin B concentrate ("prodotto X") turned silver-gray. Feeding whole grain to the rats restored the coloration back to normal.

change color together with a wide strip of hair on the back, leaving black hair only on the top of the head and on the area around the base of the tail. Finally the last-mentioned parts also become gray.

If such rats are returned to the stock diet their hair generally regains the original coloration. First the skin under the gray hair becomes blue-black and then a deposition of the pigment in the hair takes place, accompanied by a gradual disappearance of the blue-black color of the skin which becomes white again. Nevertheless, the tip and the lower third part of the hair remain gray for a certain period of time. In all cases the dark coloration of the skin precedes the darkening of the hair. (This is in line with Saccardi's histological studies on production of pigment in rabbits.)<sup>3</sup> The hairs become dark in the same sequence as they turned gray. First lower neck, portion around eyes, belly and outer parts of the extremities, then the whole back and finally the top of the head and the region around the tail become black. In rats whose diet was changed when blackish spots still remained on the top of the head and on the area around the base of the tail the color in these places was intensified simultaneously with its restoration at the parts where it normally appeared first. These changes were found very easy to follow when rats were made hairless by a diet consisting of one part by weight of honey and one part by volume of milk, although in this case the sequence was somewhat changed.

In order to ascertain whether the hemoglobin level bears any relation to the darkening of the skin, hemoglobin reading was taken simultaneously with the first appearance of the skin pigmentation. The coloration of the skin of a rat which had 8 gms of hemoglobin per 100 cc of blood appeared two days after the rat was put on the stock diet. A rat which had 3.4 gms of hemoglobin per 100 cc of blood showed first signs of darkening six days later when the hemoglobin reading was equal to 7.5 gm per 100 cc. One may consider such a coincidence at least suggestive, if not significant, since iron was found in melanin compounds.<sup>4</sup> Pough<sup>5</sup> discovered that ferrous salts in small quantity hasten the production of melanine, and Cohen and Elvehjem<sup>6</sup> demonstrated the importance of copper in an increase of the oxidase test of the liver tissue of anemic rats.

Then the question arises as to why these changes do not occur simultaneously over all the body but are localized to certain areas, anterior parts being, it appears at least, preferential. In rats, the young are born white (red), no matter whether the parents are

black or white. Pigmentation appears a few days later and starts on the anterior and lateral parts of the body, so far as the writer noticed. One is tempted to make the suggestion that this sequence in repigmentation is just a phylogenetic factor.

Not only does the hair of rats put on a milk diet become gray, but the front teeth become white as well. This is noticeable first at the end of the third week of the milk diet. The brown color of incisors begins to disappear from the base of the teeth and at the end of the fifth week of the milk diet they are usually completely white or only a small brown spot can be seen on the distal parts of the incisors. When such rats are put back on the stock diet their incisors become brown again in a 5 to 6 weeks' period. The brown color appears at the base and proceeds distally, which signifies that the pigment is deposited at the roots of the teeth.

In order to find out whether iron and copper (directly or indirectly) are responsible for the changes in the color of teeth of anemic rats a pair of such rats was changed to the iron-copper-milk diet. Unfortunately one of them died on the second day. The incisors of the other rat became normally brown nine weeks after the change of the diet. One may conclude that this experiment is suggestive enough to warrant further investigations.

It is interesting to note that when teeth first appear in a new-born rat, they are white and only later gradually become brown. It is possible that the brown pigment of incisors in Rodentia has something to do with the strength of these teeth in that family.

The writer is indebted to Dr. L. S. Palmer, of the Biochemistry Division, for making available laboratory equipment and experimental animals.

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<sup>3</sup> *Biochem. Ztschr.*, 132: 443-456, 1922.

<sup>4</sup> H. Wealsch, *Ztschr. Physiol. Chem.*, 213: 35-57, 1932.

<sup>5</sup> *Biochem. Jour.*, 26: 106-117, 1932.

<sup>6</sup> *Jour. Biol. Chem.*, 107: 97-105, 1934.